Ovarian Cancer Treatment 2014 and beyond

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The Impact of Ovarian Cancer

- Estimated incidence and mortality in the United States (2006)\(^1\)
  - 20,810 new cases
  - 15,310 deaths
- Approximately 6% of all cancer deaths in women
- 10-year survival: 8%–20\(^2\)
# Advanced Ovarian Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Median Survival (Best Arm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 22</td>
<td>Ctxn, Doxo</td>
<td>14.2 mo.</td>
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<tr>
<td>1983</td>
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<tr>
<td>GOG 47</td>
<td>Ctxn, Doxo, CDDP (CAP)</td>
<td>19.7 mo.</td>
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<tr>
<td>1986</td>
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<tr>
<td>GOG 111</td>
<td>Paclitaxel, CDDP</td>
<td>38 mo.</td>
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<tr>
<td>1996</td>
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<tr>
<td>GOG 104</td>
<td>IP CDDP</td>
<td>49 mo.</td>
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<tr>
<td>1996</td>
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<tr>
<td>GOG 114</td>
<td>IP CDDP, IP Paclitaxel</td>
<td>63 mo.</td>
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<tr>
<td>2001</td>
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<tr>
<td>GOG 172</td>
<td>IP CDDP, IP Paclitaxel</td>
<td>67 mo.</td>
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<td>2006</td>
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</tbody>
</table>
Management Points in Ovarian Cancer

Symptoms

Diagnosis

Evaluation ? SLL

Chemotherapy #1

Surgery

Maintenance

Survivorship

Progression

Secondary Surgery

Chemo #2

Chemo #3+

Supportive Care

Death
Opportunity #1

Optimal Tumor Debulking
Tumor Reductive Surgery

Defined not by the surgery performed or the amount of tumor removed but by how large the residual disease is.
Ovarian Cancer: Survival by Residual Disease

GOG Protocols (PR) 52 and 97
“It’s the Biology of the Disease”
If True, Then Patients Needing More Radical Surgery Should Do Worse

Not Radical
- TAH
- BSO
- Omentectomy
- lymphadenectomy

Radical Surgery =
- Radical TAH
- TAH and rectal resection
- splenectomy
- diaphragm surgery
- bowel resection
- extensive peritoneal stripping
IIIC and Carcinomatosis: Influence of Radical Surgery (N=144)

Radical Surgery=
- Radical TAH
- TAH and rectal resection
- splenectomy
- diaphragm surgery
- bowel resection
- extensive peritoneal stripping
Management Points in Ovarian Cancer

- Symptoms
- Chemotherapy #1
- Maintenance
- Progression
- Secondary Surgery
- Death
- Survivorship
- Supportive Care
- Diagnosis
- Evaluation ? SLL
- Surgery
- Chemo #2
- Chemo #3+
2006 meta-analysis

- included 60 trials in women (n=15,609) with EOC
- A platinum-based combination was better than platinum monotherapy (hazard ratio [HR] favoring the combination 1.16, 95% CI 0.86-1.58)
- A platinum-taxane combination was better than a platinum plus non-taxane combination (HR favoring platinum plus taxane 1.28, 95% CI 1.07-1.53)

International Study / GOG182
New Drugs, More Drugs, and New Sequences to avoid emerging drug resistance.

Regimen I (control)
Paclitaxel 175 mg/m² IV (3 h) d 1
Carboplatin AUC 6 IV d 1

Regimen II (triplet A)
Paclitaxel 135 mg/m² IV (3 h) d 1
Carboplatin AUC 5 IV d 1
Gemcitabine 800 mg/m²/d IV d 1, 8

Regimen III (triplet B)
Paclitaxel 135 mg/m² IV (3 h) d 1
Carboplatin AUC 5 IV d 1
Doxil 30 mg/m² IV d 1
Every other cycle

Regimen IV (sequential module A)
Carboplatin AUC 5 IV d 3
Topotecan 1.5 mg/m²/d IV d 1-3

Regimen V (sequential module A)
Carboplatin AUC 6 IV d 8
Gemcitabine 1000 mg/m²/d IV d 1, 8

Regimen IV (sequential module B)
Paclitaxel 175 mg/m² IV (3 h) d 1
Carboplatin AUC 6 IV d 1

Regimen V (sequential module B)
Paclitaxel 175 mg/m² IV (3 h) d 1
Carboplatin AUC 6 IV d 1

Randomization
• All patients
• Equal proportions on each regimen
• Primary end points: PFI, OS, RR

Regimens I and II: 8 cycles, 21-d cycle interval.
Regimens IV and V: 4 cycles, 21-d cycle interval.
Drug Delivery for Ovarian Cancer: Intraperitoneal Therapy

- 1950’s: First use of IP for malignant ascites
- 1968: Long-term peritoneal access device
- 1978: Demonstration of slow peritoneal clearance of some drugs
- 1984: Feasibility of intermittent large volume intraperitoneal therapy
- 1996: First report of a survival benefit for IP vs. IV chemotherapy in advanced ovarian cancer
Assumption: IP Provides Pharmacological Benefit

- Misleading
  - Measure AUC of drug in dialysate to plasma
  - Should be tumor to plasma

- Tumor penetration is superficial (1-2 mm)
- Efficacy requires good distribution

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak</th>
<th>AUC</th>
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<tbody>
<tr>
<td>Cisplatin</td>
<td>20</td>
<td>12</td>
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<td>Carboplatin</td>
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<td>18</td>
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<tr>
<td>Melphalan</td>
<td>93</td>
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<td>Adriamycin</td>
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<td>5-FU</td>
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<td>MTX</td>
<td>92</td>
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<tr>
<td>Paclitaxel</td>
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<td>1,000</td>
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<td>Study</td>
<td>Median PFS (mo)</td>
<td>HR</td>
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<tr>
<td>GOG 104</td>
<td>IV</td>
<td>IP</td>
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<tr>
<td>Alberts</td>
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<tr>
<td>GOG 114</td>
<td>41</td>
<td>49</td>
</tr>
<tr>
<td>Markman</td>
<td>(P = 0.01)</td>
<td></td>
</tr>
</tbody>
</table>
Ovarian Cancer: IP Chemotherapy

**GOG 172**

**Randomize**

Epithelial ovarian carcinoma, Optimal (<1cm) stage III, or Primary peritoneal cancer
Stratified by presence of gross residual disease and planned second-look laparotomy.

**Blood Draw for BRCA Analysis**

**Paclitaxel**
135 mg/m² IV over 24 hrs day 1, q 21 days x 6

**Cisplatin**
75 mg/m² IV day 2, q 21 days x 6

**Second look Laparotomy (if chosen)**

**Paclitaxel**
135 mg/m² IV over 24 hrs, day 1, q 21 days x 6

**Cisplatin**
100 mg/m² IP day 2, q 21 days x 6

**Paclitaxel**
60 mg/m² IP, day 8, q 21 days x 6
GOG-172 Survival

GOG #172: Overall Survival

![Graph showing survival rates comparing intraperitoneal and intravenous therapy. The graph indicates a statistically significant difference (P=0.03) in survival rates between the two treatment methods. The survival rates for intraperitoneal therapy are consistently higher than those for intravenous therapy from the start of the study.]
GOG 172: Toxicity

Hematologic

Non-Hematologic

WBC, PLT, Infection

Infection, GI, Renal, Fatigue, Pain, Metabolic, Neuro
Quality of Life: GOG 172

![Graph showing quality of life metrics over time with IV and IP treatments and statistical significance levels: P = 0.03, P < 0.001, P = 0.009, P = NS for different time points: Pretreatment, 4th Cycle, Post-treatment 3-6 wks, Post-treatment 12 mos.](image-url)
Number of IP Courses Completed

Courses Completed

- 0 courses: 8
- 1 course: 92
- 2 courses: 74
- 3 courses: 59
- 4 courses: 52
- 5 courses: 47
- 6 courses: 42

Walker, Gynecol Oncol. 100:27, 2006
Advanced stage ovarian cancer

Conventional Regimen
Six cycles paclitaxel (180 mg/m², 3-h IV) plus carboplatin (AUC 6), given on day 1 of a 21-day cycle

Dose-dense Regimen
Six cycles paclitaxel (80 mg/m²; 1-h IV) given on days 1, 8, and 15 plus carboplatin given on day 1 of a 21-day cycle
JAPANESE GOG

- 631 total
  - Dose-dense regimen, 312
  - Conventional regimen, 319

- Toxicity
  - Dose-dense regimen group n=113
  - Conventional regimen group n=69
  - Neutropenia
    - dose-dense regimen, 286 [92%] of 312
    - conventional regimen, 276 [88%] of 314
  - Grade 3 and 4 anemia
    - Dose-dense treatment group (214 [69%])
    - Conventional treatment group (137 [44%])
    - p<0.0001
Advancing stage ovarian cancer

Conventional Regimen
Six cycles paclitaxel (180 mg/m², 3-h IV) plus carboplatin (AUC 6), given on day 1 of a 21-day cycle
PFS 17.2m
3 YR SURVIVAL 65.1%

Dose-dense Regimen
Six cycles paclitaxel (80 mg/m², 1-h IV) given on days 1, 8, and 15 plus carboplatin given on day 1 of a 21-day cycle
PFS 28.0m*
3 YR SURVIVAL 72.1%*

Advanced stage ovarian cancer suboptimal

Conventional Regimen
Six cycles paclitaxel (175 mg/m2, 3-h IV) plus carboplatin (AUC 6), given on day 1 of a 21-day cycle

Dose-dense Regimen
Six cycles paclitaxel (80 mg/m2; 1-h IV) given on days 1, 8, and 15 plus carboplatin given on day 1 of a 21-day cycle
GOG #252

OPTIMAL & SUBOPTIMAL STAGE III & IV

STANDARD IP
IV TAXOL 135MG/M2 X3HRS

DOSE DENSE IV

COMBINATION
Incorporation of angiogenesis inhibitors
GOG #218

STAGE III OR IV WITH GROSS RESIDUAL TUMOR

CARBO AUC 6 TAXOL 175MG/M2 PLACEBO

CARBO AUC 6 TAXOL 175MG/M2 BEVACIZUMAB

PLACEBO

PLACEBO

BEVACIZUMAB

9/05-8/09
At a median followup of 17 months, there was no difference in PFS between group II and group I (median PFS, 10 and 11 months, respectively).

Compared to group I, there was a significant increase in the median PFS in group III (14 months).

There was no improvement in OS; median OS across all arms was approximately 39 months.

The incidence of GI perforation or fistula formation was 3 percent in both bevacizumab containing arms versus 1 percent in the chemotherapy alone arm.
Incorporation of angiogenesis inhibitors

- The National Comprehensive Cancer Network (NCCN) does not recommend bevacizumab routinely as part of the initial adjuvant therapy or as maintenance therapy following adjuvant therapy of advanced stage EOC.

- Although actual cost data were not collected in GOG-218, a subsequent modeled cost-effectiveness analysis using the available data on PFS and OS concluded that the cost-effectiveness ratio for the addition of bevacizumab to standard chemotherapy was unfavorable.

GOG #3001

- Angiopoietin 1,2
- AMG 386
- Toxicity profile distinct from VEGF
Management Points in Ovarian Cancer

- Symptoms
- Diagnosis
  - Evaluation? SLL

- Surgery
- Chemotherapy #1
- Maintenance
  - Progression
  - Secondary Surgery

- Chemo #2
- Chemo #3+
  - Death

- Supportive Care
- Survivorship
Why Maintenance?

- Recurrence after clinical CR: 50-80%
- Recurrence after pathological CR: 40-60%
- Prognostic factors for recurrence:
  - Tumor burden = residual disease
  - Response to therapy = “biology”
  - Unknowns
- Cure after Recurrence: Rare
Maintenance Therapy: Ovarian Cancer

**Symptoms** → **Chemotherapy #1** → **Maintenance** → **Progression** → **Secondary Surgery** → **Chemo #2** → **Chemo #3+** → **Death**

- Options:
  - Radiation
  - Immunotherapy
  - Extension of first-line therapy
  - Novel agents
  - High-Dose (stem cell)
  - Intraperitoneal (chemotherapy, radiation, immunotherapy, etc)
  - Vaccine

**Supportive Care**
Consolidation or Maintainence chemotherapy

- What has been shown in clinical trials that appears to help:
  - Oral altretamine
  - IV Taxol monthly

- What has not helped:
  - Five day topotecan as consolidation
  - Ovarex
  - Interferon
  - Whole Abdomen Radiation.
  - 12 cycles instead of 6
  - High dose chemotherapy
  - $^{32}$P
SWOG-9701 / GOG 178
Consolidation Trial: Schema

Eligibility:
• Stage III-IV
• Clinically NED following platinum/paclitaxel
• No 2nd-look surgery

Assign to:
Paclitaxel 135 mg/m² over 3 hrs Q 28 D x 3 cycles
Paclitaxel 135 mg/m² over 3 hrs Q 28 D x 12 cycles

Closed at Interim Analysis November 2001 by DSMB because the PFI for the 3 cycle arm was 21 mos vs 28 mos for the 12 cycle arm with HR of 2.3 and p=0.0035
Oregovomab (Ovarex™)

Ovarian Cancer
Clinical CR
Normal CA125

Placebo  Ovarex™

Outcome: TTP, OS

Fig 1. Kaplan-Meier curve of time-to-disease relapse from the time of randomization for the modified intent-to-treat population. Median progression-free survival: oregovomab (n = 73; 48 events), 13.3 months; placebo (n = 72; 48 events), 10.3 months. P = .71 (log-rank test).

Berek J Clin Oncol 22:3507, 2004
Interferon-α Maintenance
Interferon-α Maintenance

Median survival
Interferon = 27.0 months
Observation = 32.7 months
Unadjusted HR = 1.06 (0.82 – 1.38)
Log-rank test $P = 0.65$

$P$-value for Log-rank test = 0.65

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<tr>
<th>Time since randomisation (months)</th>
<th>Observation</th>
<th>Interferon</th>
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<td>156</td>
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Vaccination Strategy Using Treg Depletion
Management Points in Ovarian Cancer

Diagnosis

Symptoms

Chemotherapy #1

Evaluation

Evaluation

SLL

Progression

Surgery

Secondary Surgery

Chemo #2

Chemo #3+

Supportive Care

Death

Maintenance

Survivorship
Recurrent Ovarian Cancer: Definition of Disease Sensitivity

Time to Recurrence, Months

0 3 6 12 18 24 X

- Refractory
- Resistant
- Sensitive
- Really, Really Sensitive
The challenges to studying recurrent ovarian cancer

- Treatment (platinum) free interval predicts response more than which agent is used.
- Unique activity is best established in platinum resistant disease where a RR>20% is exciting.
- For third line platinum resistant pt 10%RR suggests activity.
- The end point should be PFS, very difficult to study OS when more tx to follow
Secondary Response to Platinum

- \( N = 176 \) pts
- Accrual: 1993-2003
  - Responders = 125/211 regimens (55%)
  - TFI_1 is related to response but not predictive individually
- TFI_2 < TFI_1 (\( N = 114, 97\% \))
  - 3/4 exceptions received different chemo agents with platinum

Treatment-Free Interval and Survival

- \( N = 583 \) pts
- Phase II/III GINECO trials
- RECIST criteria of response
- Independent response effects (no prediction of response on the basis of prior drug or response to regimen)

Lauraine, Proc ASCO #829, 2002
Therapeutic Options for Ovarian Cancer

<table>
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<tr>
<th>Drug</th>
<th>Platinum-Resistant</th>
<th>Platinum-Sensitive</th>
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<tr>
<td>Docetaxel</td>
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<td>Doxil</td>
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<tr>
<td>Etoposide</td>
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<tr>
<td>Gemcitabine</td>
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<tr>
<td>Paclitaxel</td>
<td>10%–25%</td>
<td>20%–55%</td>
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<tr>
<td>Platinum</td>
<td></td>
<td></td>
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<tr>
<td>Topotecan</td>
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<tr>
<td>Vinorelbine</td>
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**Gem/CARBO vs. CARBO: Design**

- Recurrent Ov Ca
- 6+ mos after platinum
- Strata:
  - PFI (6-12, > 12 mos)
  - 1st-line therapy (Platinum +/- Paclitaxel)
  - Measurable vs. Evaluable
- Primary Endpoint = PFS

**Randomization**

- Gemcitabine 1000 mg/m² d 1+8
- Carboplatin AUC 4 d 1 q 21 x 6 (-10)
- Carboplatin AUC 5 d 1 q 21 x 6 (-10)

Progression-Free Survival

HR = 0.72 (95% CI 0.58 - 0.90)
Log-rank p-value = 0.0031

Median = 5.8m (5.2 - 7.1m)
Median = 8.6m (7.9 - 9.7m)

Pts at risk
Cb 178 pts / 162 evts
GCb 178 pts / 163 evts

ASCO '04 #5005
HR = 0.96 (95% CI 0.75 – 1.23)
Log-rank p-value = 0.7349

Med = 17.3m (15.2 - 19.3m)
Med = 18.0m (16.2 - 20.2m)

Trial not powered for OS
ICON IV: Schema

Relapsed ovarian or primary Peritoneal requiring chemotherapy
Previous platinum-based chemotherapy

Prior chemotherapy:
- Carboplatin (34%)
- Cisplatin (30%)
- Paclitaxel/platinum (36%)

TFI: >12 mos for 75%

Conventional platinum-based chemotherapy
Paclitaxel plus platinum Chemotherapy

ICON IV: Survival

Progression-free survival (PFS)

- Hazard ratio = 0.76
  (95% CI 0.66 - 0.89; p < 0.001)
- Absolute difference at 1 year = 10%
  (40% to 50%; 95% CI 4% to 15%)
- Median PFI: 9 vs. 12 mos

Overall survival (OS)

- Hazard ratio = 0.82
  (95% CI 0.69 - 0.97; p = 0.023)
- Absolute difference at 2 years = 7%
  (50% to 57%; 95% CI 1% to 12%)
- Median OS: 24 vs. 29 mos

Median Follow-up: 42 mos
OR: 54 vs. 66% (P = 0.06)
Platinum Combinations: Summary

- Combination strategies appear to produce superior response rates and PFS
- Overall survival is the “bar”
- Unclear if sequential administration will reach the same endpoint
- QoL and toxicity are mandatory secondary endpoints
Neoadjuvant Chemotherapy

- giving pts 3-4 cycles of chemotherapy prior to debulking surgery
- Easier surgery
- Less hospital days
- Survival data mixed
EORTC/NCIC Neoadjuvant Chemotherapy

- 670 women with stage IIIIC/IV EOC
- No difference in progression-free survival (PFS, 12 months in both groups)
- Similar overall survival in the neoadjuvant treatment group compared to those who underwent initial surgery (29 and 30 months)
- Lower rate of complications as compared to initial surgery

SEER Database and Neoadjuvant Chemotherapy

- 6844 women in this retrospective trial
- Significantly fewer ostomies placed (7.8 vs 19.2 percent), less small bowel resections (3.8 versus 6.3 percent), and less large bowel resections (11.1 versus 20.6 percent).
- Significant reduction in postoperative complications
- Among women with stage III disease, the risk of death at two years was higher following neoadjuvant chemotherapy [RR] 1.16
- For women with stage IV EOC, there was a reduction in the risk of death at two years associated with neoadjuvant chemotherapy [RR] 0.85

Gynecol Oncol. 2011;123(3):461
In vitro chemosensitivity and resistance assays

- Chemo-FX assay or the Extreme Drug Resistance (EDR) assay
- ASCO concluded that the evidence is insufficient to justify the routine use of any of these assays
- Oncologists should make chemotherapy treatment recommendations on the basis of published clinical trial reports

J Clin Oncol. 2011;29(24):3328
PARP INHIBITORS

- Inhibitors of poly ADP ribose polymerase
- PARP1-protein important in repairing SS breaks—when these are not repaired DS breaks are formed with replication
- PARP inhibitors—cause multiple double strand breaks and tumors that have BRCA 1, BRCA 2 mutations cannot repair these and causes cell death
- Other cells sensitive to PARP inhibitors include tumors with PTEN mutations, PLAB2, radio sensitizers
Role of CA-125 surveillance

- Medical Research Council (MRC) 05 trial. In this study, 1442 women had their CA-125 levels checked every three months.
- Asymptomatic but whose CA-125 levels exceeded twice the upper limit of normal (n = 527) were randomly assigned to immediate treatment or to treatment at the time of a clinical or symptomatic recurrence.
Role of CA-125 surveillance

- Medical Research Council (MRC) 05 trial. In this study, 1442 women had their CA-125 levels checked every three months.
- Asymptomatic but whose CA-125 levels exceeded twice the upper limit of normal (n =527) were randomly assigned to immediate treatment or to treatment at the time of a clinical or symptomatic recurrence.
- Second-line chemotherapy was started a median of five months earlier.
- This did not contribute to improved survival.
- Immediate treatment had an adverse impact on quality of life.
Role of CA-125 surveillance

- Following patients longitudinally by CA-125 may help identify patients for surgical treatment at recurrence.
- A shorter time to surgery measured from the initial rise in CA-125 was associated with improved surgical outcome; the time from initial CA-125 elevation to surgery was five weeks in those optimally cytoreduced versus 16 weeks for those who were not.

Gynecol Oncol. 2011;121(2):249
DFS

- Stage I & 2: 65-90%
- Stage III optimal: 40%
- Stage III sub optimal: 5-10%
- Stage IV: 5-10%
Screening

- Unknown precancer condition
- Low detection
- High mortality
- No screening has yet proven to be effective
Prevention

- OCP
- Tubal Ligation
- Prophylactic Oophorectomy
OCP

- 6 years of use
- 60% Reduction

Tubal Ligation

- ↓ Risk in General Population
- BRCA1 0.39 (0.22 - 0.70)
- Both TL + OCP 0.28 (0.15 - 0.50)
Risk of Ovarian Cancer

General Population 1.4%
BRCA1 16-60%
BRCA2 10-25%
Prophylactic Salpingo-Oophorectomy

551 Women w/ BRCA1 or 2 mutation
- **292 Control Group**
  - 58 Cancers
  - 6/58 Stage I (11%)
- **259 PO**
  - 6 Stage I Ovarian Ca
  - 2 Additional Peritoneal Ca
- **Risk Decreased from 20% to < 1%**
- **RR Breast CA .45 (.29 - .77)**

Rebbeck NEJM 2002
3 Unanswered Issues:

1) Optimal Time
2) Should Hysterectomy be included
3) Role of HRT
Optimal Time

- Deferred until childbearing complete
- BRCA 1 patients – 11-21% CA risk by age 50
- Defer till > 40 may lose breast protection
- 2-4% rate of occult invasive carcinoma
Hysterectomy

- No consensus
- Should include bilateral salpingectomy
- Argue... portion of tube in uterus is at theoretical risk
- Uterine cancer not over represented in BRCA2
- Uterine cancer may be increased in BRCA1
  - [1-2%]
- Increase morbidity
Estrogens

I just don’t know what to think
HRT Effect on Breast Cancer Reduction

- Cohort of never users  RR 0.42
- Cohort of users & nonusers  RR 0.53
HRT Effect on Breast Cancer Reduction

- Cohort of never users: RR 0.42
- Cohort of users & nonusers: RR 0.53
The Christl Burgess Memorial Fund Lectureship presents

OVARIAN CANCER: AN OUNCE OF PREVENTION

PRESENTED BY

Robert J. Kurman, MD

Robert J. Kurman, MD, is an accomplished physician, professor and research investigator and one of the world's leading pathologists. He is considered a national and international authority in the field of ovarian pathology. His groundbreaking work in ovarian cancer has led to a new model that may lead to earlier detection of malignant disease. Dr. Kurman is the Richard W. TeLinde Distinguished Professor of Gynecologic Pathology, Departments of Gynecology & Obstetrics, Pathology, and Oncology, The Johns Hopkins University School of Medicine and Hospital.

THURSDAY, MAY 22, 2014

5–6 p.m. Reception and light refreshments
6–7 p.m. Lecture program

Loyola University Medical Center
Stritch School of Medicine, Tobin Hall
2160 S. First Ave.
Maywood, IL 60153
# Summary of Phase III Single Agent Trials: Recurrent Ovarian Cancer

<table>
<thead>
<tr>
<th>Drug A</th>
<th>Drug B</th>
<th>N</th>
<th>TTP (wks)</th>
<th>P</th>
<th>OS (wks)</th>
<th>P</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topotecan</td>
<td>Paclitaxel</td>
<td>226</td>
<td>23 vs 14</td>
<td>NS</td>
<td>61 vs. 43</td>
<td>NS</td>
<td>Cross-over confirmed in 50%</td>
</tr>
<tr>
<td>Paclitaxel (bolus)</td>
<td>Paclitaxel (weekly)</td>
<td>208</td>
<td>38 vs 26</td>
<td>NS</td>
<td>64 vs. 59</td>
<td>NS</td>
<td>Less toxicity (wkly), no diff HSR</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Paclitaxel</td>
<td>86</td>
<td>12 vs. 14</td>
<td>NS</td>
<td>42 vs. 37</td>
<td>NS</td>
<td>74% of cohort Plat-resistant</td>
</tr>
<tr>
<td>PLD</td>
<td>Topotecan</td>
<td>481</td>
<td>16 vs 17</td>
<td>NS</td>
<td>60 vs 57</td>
<td>NS</td>
<td>54% Plat-resist; PLD OS benefit in plat-sensitive subgroup</td>
</tr>
<tr>
<td>PLD</td>
<td>Paclitaxel</td>
<td>214</td>
<td>22 vs 22</td>
<td>NS</td>
<td>46 vs. 56</td>
<td>NS</td>
<td>All patients taxane-naïve</td>
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<tr>
<td>Topotecan</td>
<td>Treosulfan</td>
<td>357</td>
<td>22 vs 12</td>
<td>0.001</td>
<td>56 vs. 48</td>
<td>0.02</td>
<td>2nd-3rd line, Topo more heme</td>
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<tr>
<td>PLD</td>
<td>Gemcitabine</td>
<td>195</td>
<td>16 vs 13</td>
<td>NS</td>
<td>PEND</td>
<td>Cross-over Design</td>
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<td>SGO 2006</td>
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</tbody>
</table>

Comment:
- All patients taxane-naïve
- 2nd-3rd line, Topo more heme
- All Plat-resistant
- Gr 3/4 PPE, mucositis
- (PLD), Gr 3/4 Heme

N: Number of patients
TTP: Time to Progression
OS: Overall Survival
P: Significance Level
NS: Not Significant